UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF NORTH CAROLINA
CHARLOTTE DIVISION
3:22-MD-03036-KDB

IN RE: GARDASIL PRODUCTS LIABILITY LITIGATION	)	**MDL No. 3036**
	)	**THIS DOCUMENT RELATES TO ALL BELLWETHER CASES**

DEFENDANTS' MEMORANDUM IN SUPPORT OF MOTION TO EXCLUDE THE EXPERT TESTIMONY OF DR. MARTIN KULLDORFF PURSUANT TO FEDERAL RULE OF EVIDENCE 702

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INTRODUCTION

Plaintiffs' lone biostatistical expert, Dr. Martin Kulldorff, has previously performed and authored studies on Gardasil's safety and—as recently as 2021—has published that his studies showed "no specific serious adverse events" and his findings "should provide reassurance about this vaccine's safety."[1] As a result, and perhaps not surprisingly, Dr. Kulldorff agreed at his deposition he is ***not*** providing opinions on the central issue in this litigation: general causation. Dr. Kulldorff admitted he cannot give a "definite view" on "whether the epidemiologic data available today shows that Gardasil causes POTS or POI," and nor was he "asked to do so as part of this litigation." Ex. 2, Kulldorff Dep. Tr. at 24:7–12. Dr. Kulldorff's expert report does not contain any opinions on whether Gardasil causes POTS or POI, and he declined to draw any conclusions on general causation because, as he admitted, he has not "read the complete literature that's necessary to provide such an opinion." *Id.* at 53:2–15; 54:10–22. Thus, as an initial matter, the Court need not consider Dr. Kulldorff's opinions in its decision on general causation.

At the same time, Dr. Kulldorff's testimony revealed that the Court should restrict the limited opinions he does purport to offer. Merck thus moves to exclude Dr. Kulldorff from testifying on ***two*** discrete topics.

First, the Court should bar any testimony from Dr. Kulldorff regarding Merck's conduct or actions in 2015 in response to the Article 20 procedure of the European Medicines Agency ("EMA"). The EMA invokes Article 20 when it wants to investigate further the safety or efficacy of a medicine, and the procedure requires the manufacturer to respond to the EMA's questions. In various ways, Dr. Kulldorff's deposition testimony undermined his conclusions about Merck's

[1] Ex. 1, Yih 2021 (Kulldorff Dep. Ex. 24) at 1253.

Article 20 response to the EMA, revealing that he used an unreliable methodology to draw those conclusions.

Second, Dr. Kulldorff should not be allowed to opine about the disproportionality analysis performed by Plaintiffs' general causation expert, Dr. Lucija Tomljenovic, which she conducted in 2024 for purposes of this litigation. A disproportionality analysis is "an industry standard pharmacovigilance technique used to detect and evaluate safety signals—that is, the existence of an excess of reported adverse medical events." *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1345 (N.D. Fla. 2018). Dr. Kulldorff's opinions about her analysis were essentially restricted to "checking her math" and thus merely parrot Dr. Tomljenovic's conclusions. Simply repeating another expert's conclusions is not proper. Even if it were, Dr. Tomljenovic testified that her disproportionality analysis is not evidence of causation. As a result, at minimum, the Court should prevent Dr. Kulldorff from suggesting that Dr. Tomljenovic's litigation-derived disproportionality analysis performed in 2024 is anything more than the signal generation tool confirmed by Dr. Tomljenovic.

BACKGROUND

Dr. Martin Kulldorff is the only biostatistician disclosed by Plaintiffs. Ex. 3, Kulldorff Rpt. at 1. He is not a medical doctor and has never had any formal medical training. Ex. 2, Kulldorff Dep. Tr. at 22:12–15. Dr. Kulldorff was previously a professor of medicine at Harvard Medical School and affiliated with the Mass General Brigham hospital system. *Id.* at 14:12–15:11.

Dr. Kulldorff helped develop and implement statistical methods used by the Food and Drug Administration ("FDA") and Centers for Disease Control and Prevention ("CDC") to monitor vaccine safety, including the safety of Gardasil. Ex. 2, Kulldorff Dep. Tr. at 61:7–19. He is a former member of the FDA's Drug Safety and Risk Management Advisory Committee and the

CDC's Vaccine Safety Subgroup of the Advisory Committee on Immunization Practices, although he did not evaluate Gardasil in either of these positions. *Id.* at 15:12–19, 16:18–17:5.

Dr. Kulldorff has previously researched the safety of Gardasil and published, on multiple occasions, that Gardasil is safe. As a sampling of his publications:

- In 2011, Dr. Kulldorff co-authored a "post-licensure safety assessment of quadrivalent human papillomavirus vaccine" that studied whether associations existed between Gardasil and outcomes like appendicitis, Guillan-Barré Syndrome, stroke, venous thromboembolism, seizures, syncope, allergic reactions, and anaphylaxis. Ex. 4, Gee 2011 (Kulldorff Dep. Ex. 5) at 8279. After confirming that "[p]relicensure clinical trials have shown no evidence for any major safety problems," the paper concluded there was "no statistically significant increased risk for the outcomes studied." *Id.*

- In 2018, after studying 1.9 million Gardasil recipients, Dr. Kulldorff concluded that his study "did not suggest any previously unknown vaccine safety problem," and his findings "add significantly to the growing safety record of [Gardasil]." Ex. 5, Yih 2018 (Kulldorff Dep. Ex. 7) at 1269.

- In 2021, as noted above, Dr. Kulldorff co-authored a "data-mining study of almost half a million [Gardasil 9] vaccinations that followed patients up to 1 year after vaccination." Ex. 1, Yih 2021 (Kulldorff Dep. Ex. 24) at 1258. Dr. Kulldorff and his co-authors concluded that "[c]onsidering the broad scope of the evaluation and the high statistical power, the findings of no specific serious adverse events should serve to reassure those concerned about the safety of this vaccine." *Id.*

Despite his published views on Gardasil's safety, Dr. Kulldorff did not disclose any opinions—at least, in this litigation—on whether Gardasil causes POTS, POI, or any other alleged condition. Ex. 2, Kulldorff Dep. Tr. at 54:10–22. His expert report instead purports to offer three limited opinions in this case:

First, Dr. Kulldorff critiques the Chao 2012 publication, which relayed the findings of one of Merck's post-licensure commitments to continue studying the safety of Gardasil. Dr. Kulldorff levels various criticisms of the paper's methodology but ultimately concludes that the "Chao paper contributed nothing regarding potential adverse reactions to the Gardasil vaccine, ***in either direction***." *See* Ex. 3, Kulldorff Rpt. at 14–23, 24 (emphasis added). Put simply, Dr. Kulldorff argues that Chao 2012 "shows evidence of nothing." Ex. 2, Kulldorff Dep. Tr. at 266:10–16. For

purposes of the general causation inquiry, the Chao 2012 publication did not investigate POTS or POI as a specific outcome.

Second, Dr. Kulldorff criticizes Merck's actions in response to the EMA's Article 20 procedure. In July 2015, the EMA launched an Article 20 procedure to investigate a potential connection between Gardasil and POTS or complex regional pain syndrome (CRPS). In response to the EMA's questions, Merck submitted a 188-page answer to the EMA's questions. At the conclusion of the proceeding, which evaluated not only Merck's response, but numerous other sources of data, the EMA issued a lengthy report concluding that "available data do not provide support for a causal relation between HPV vaccines and POTS." Ex. 6, EMA November 2015 Assessment Report (Kulldorff Dep. Ex. 21) at 38–40. Dr. Kulldorff criticizes two specific aspects of Merck's response: (1) the types of analyses Merck conducted; and (2) Merck's methodological choices in those analyses. *See* Ex. 3, Kulldorff Rpt. at 3–9.

Third, Dr. Kulldorff offers the opinion that the calculations contained in the disproportionality analysis performed in 2024 by Dr. Lucija Tomljenovic, one of Plaintiffs' other experts, are correct. Ex. 3, Kulldorff Rpt. at 9–13. But Dr. Kulldorff did not conduct "any research on [his] own" for his opinions on her analysis—he merely repeats her findings and concludes that her calculations were correct. *Id.* at 11; Ex. 2, Kulldorff Dep. Tr. at 142:16–143:8.

This motion seeks to exclude the second and third of these three opinions.

LEGAL STANDARD

Federal Rule of Evidence 702 limits the expert testimony that may be introduced at trial. Under Rule 702, a party may call an expert to testify only if the party demonstrates that: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert's opinion

reflects a reliable application of the principles and methods to the facts of the case. Fed. R. Evid. 702. "Rule 702 thus imposes a special gatekeeping obligation on the trial judge to ensure that an expert's testimony rests on a ***reliable*** foundation and is ***relevant*** to the task at hand." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 281 (4th Cir. 2021) (cleaned up) (emphasis in original). An expert opinion is reliable if it is "supported by adequate validation to render it trustworthy," *Bourne ex rel. Bourne v. E.I. DuPont de Nemours & Co.*, 85 F. App'x 964, 966 (4th Cir. 2004), and relevant if it has "a valid scientific connection to the pertinent inquiry," *Sardis*, 10 F.4th at 281. Because expert testimony can be "powerful and quite misleading," the importance of excluding irrelevant or unreliable testimony "cannot be overstated." *Id.* at 283 (citations omitted).

ARGUMENT

Dr. Kulldorff's deposition revealed limitations in his ability to testify about Merck's response to the EMA's Article 20 inquiry and about Dr. Tomljenovic's 2024 disproportionality analysis. As a result, Merck moves to exclude his testimony on these subjects.

I. The Court should not allow Dr. Kulldorff to testify about Merck's actions in response to the EMA's Article 20 procedure.

Dr. Kulldorff should not be permitted to testify about Merck's response to the EMA's Article 20 inquiry because not only is his opinion irrelevant to this stage of the litigation, but also because his methodology is flawed.

To begin with, Dr. Kulldorff's opinions about Merck's conduct during the EMA's Article 20 inquiry are irrelevant to general causation. While Dr. Kulldorff argues that Merck should have performed different analyses and used a different background rate in its calculations when responding to the EMA's questions, Ex. 3, Kulldorff Rpt. at 6, Dr. Kulldorff does not opine that either of those alleged issues somehow shows that Gardasil increases the risk of POTS and POI. So Dr. Kulldorff's opinions about Merck's conduct in this regulatory inquiry lack a "scientific

connection" to the "pertinent inquiry before the Court," which is general causation. *See Garlinger v. Hardee's Food Sys., Inc.*, 16 F. App'x 232, 236 (4th Cir. 2001) (affirming exclusion of expert whose testimony did not "fit" the case). Dr. Kulldorff's opinions are thus irrelevant at this stage of the litigation.

But even if Dr. Kulldorff's opinions about Merck's response to the Article 20 procedure were somehow relevant (which they are not), his opinions should nevertheless be excluded because they are unreliable. As noted in his expert report, Dr. Kulldorff lodges two primary complaints about Merck's response to the EMA's Article 20 procedure: (1) instead of performing an "observed versus expected" analysis that the EMA requested, Merck should have conducted a disproportionality analysis, and (2) in performing the "observed versus expected analysis," Merck should have used a different background rate for POTS to determine the "expected" portion of the calculation. But Dr. Kulldorff used an unreliable methodology in drawing both these conclusions.

First, Dr. Kulldorff opines that Merck should have conducted a disproportionality analysis in response to the EMA inquiry, but he reviewed only one document in drawing this conclusion: "the Merck response to the Article 20 [procedure] that was provided to [him]." Ex. 2, Kulldorff Dep. Tr. at 190:10–15. And at his deposition, Dr. Kulldorff acknowledged that the Danish Health and Medicines Authority had ***already provided*** a disproportionality analysis to the EMA in April 2015, just a few months prior to the EMA's questions to Merck. *See* Ex. 2, Kulldorff Dep. Tr. at 187:14–18 (acknowledging that the EMA "obviously had this analysis before they put it into their assessment report"). The results of this analysis are detailed in the EMA's report on Article 20. *See generally* Ex. 6, EMA November 2015 Assessment Report (Kulldorff Dep. Ex. 21) at 27. Thus, the EMA did not need Merck to conduct a disproportionality analysis, since they already had one—

which reveals Dr. Kulldorff used an unreliable methodology in faulting Merck for not conducting such an analysis.

What is more, in its EMA reply, Merck performed the requested "observed versus expected" analysis, which compares "the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population." Ex. 3, Kulldorff Rpt. at 5. Dr. Kulldorff admitted at his deposition that the EMA's questions to Merck in fact ***required*** Merck to conduct the "observed versus expected" analysis he criticizes.[2] He acknowledged that "very specific questions were asked of Merck by the EMA" during the Article 20 procedure. *See* Ex. 2, Kulldorff Dep. Tr. at 193:14–17. One of those questions was to "conduct the observed versus expected analysis." *Id.* at 202:15–19, 203:23–25; *see also* Ex. 3, Kulldorff Rpt. at 5 (describing how Merck was "tasked" with performing this analysis). And Dr. Kulldorff is "not an expert on the EMA system," so he has no opinion that Merck could have simply ignored this request from a regulator. *Cf.* Ex. 2, Kulldorff Dep. Tr. at 169:22–25. So there is a clear "analytical gap" between Dr. Kulldorff's testimony, which opines that Merck should not have performed this analysis, and the material on which Dr. Kulldorff relies, which acknowledges that Merck was required to perform it. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Second, Dr. Kulldorff's admissions at his deposition also undermine his criticism of Merck's selection of the "background rate," which is the rate that the conditions being studied are expected in the general population and is used as the "expected" rate in the "observed versus expected" analysis. He claims in his expert report that the background rates Merck used were

[2] The EMA consulted with the Scientific Advisory Group on vaccines in connection with the Article 20 procedure, and with respect to Merck's observed vs. expected analysis, they concluded that it was "as robust as it could be, given the difficulties with the type of data gathered and the assumptions made." Ex. 6, EMA November 2015 Assessment Report (Kulldorff Dep. Ex. 21) at 32, 34.

"flawed" due to "uncertainties both in the estimated denominator (number of people exposed to the vaccine[]) and in the numerator (background rate of the number of observed cases among the unexposed)." Ex. 3, Kulldorff Rpt. at 6. But when it was put to him directly, Dr. Kulldorff could not "cite a different background rate for POTS that Merck should have used" instead. Ex. 2, Kulldorff Dep. Tr. at 204:25–205:3. At his deposition, Dr. Kulldorff admitted he actually had to "give credit" to Merck because "there wasn't really anything good to choose between." *Id.* at 204:6–13. And he couldn't "really blame Merck" for choosing the rate it did. *Id.* at 204:6–13. Thus, there is yet another "analytical gap" between Dr. Kulldorff's conclusion in his expert report (that Merck's choice of background rate was flawed) and his actual testimony (that he couldn't blame Merck for using the rate it did). *Joiner*, 522 U.S. at 146.

All told, Dr. Kulldorff's deposition testimony showed he lacks a reliable basis for his opinions. Dr. Kulldorff's opinions on Article 20 suffer from methodological problems, as shown by his own deposition admissions—including that Dr. Kulldorff did not consider all the information available on the subject, and that the material on which he relies does not support his conclusions. His testimony on this subject should thus be excluded.

II. The Court should not allow Dr. Kulldorff to testify about Dr. Tomljenovic's disproportionality analysis.

Dr. Kulldorff should not be permitted to testify at all about Dr. Tomljenovic's 2024 disproportionality analysis because his opinion merely parrots her litigation report, which is not the proper role of expert testimony. But even if he is allowed to testify on the subject, the Court should preclude Dr. Kulldorff from testifying that Dr. Tomljenovic's analysis somehow supports

an association between Gardasil and POTS/POI, since Dr. Tomljenovic herself has testified her study is useful only for safety signal generation,[3] not hypothesis testing.

Dr. Kulldorff's report inappropriately regurgitates the data used in Dr. Tomljenovic's disproportionality analysis. An expert "may not merely parrot the conclusion of another expert." *Wilhelm v. Ameristep Corp.*, 2018 WL 6272911, at *15 (W.D. Va. Nov. 30, 2018). Rather, experts must perform their own independent analysis instead of "regurgitat[ing]" another expert's findings. *In re Davol, Inc./C.R. Bard, Inc., Polypropylene Hernia Mesh Prod. Liab. Litig.*, 546 F. Supp. 3d 666, 676 (S.D. Ohio 2021); *see also Ask Chemicals, LP v. Computer Packages, Inc.*, 593 F. App'x 506, 510 (6th Cir. 2014) (rejecting expert's "wholesale adoption" of another's opinions or estimates because it "cloaks unexamined assumption in the authority of expert analysis"). In short, an expert cannot merely "accept[]" another expert's work and "incorporat[e] it into a report." *See Auto Indus. Supplier Emp. Stock Ownership Plan (ESOP) v. Snapp Sys., Inc.*, No. 03-74357, 2008 WL 5383372, at *5 (E.D. Mich. Dec. 23, 2008). Such testimony "simply does not meet the reliability component necessary for expert testimony." *Id.*

Dr. Kulldorff did not independently investigate the underlying evidence and did not conduct "any research on [his] own" for his analysis of Dr. Tomljenovic's calculations, Ex. 2, Kulldorff Dep. Tr. at 142:16–143:8. Nor did he:

- Assess the adequacy of the database query terms, *id.* at 219:9–22;

[3] Analyses of adverse event reports can sometimes generate a "safety signal," which is information on an adverse event that "requires further investigation." Ex. 7, EMA, Glossary of Regulatory Terms – Safety Signal, https://www.ema.europa.eu/en/glossary-terms/safety-signal. But identification of a safety signal is only "a potential safety issue" and does not mean that "a causal relationship between the drug and the [] risk" exists. Ex. 8, FDA, Potential Signals of Serious Risks, available at https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system

- Verify Dr. Tomljenovic's counting of events, *id.* at 220:12–14; or
- Perform a chart or clinical review of her analysis, *id.* at 213:4–24.

All Dr. Kulldorff did was "check[]" that Dr. Tomljenovic did her "statistical calculations" "correctly" and verify that the results were "logical." Ex. 3, Kulldorff Rpt. at 11. As a result, Dr. Kulldorff's opinion is the kind of "wholesale adoption" of another expert's opinion that should not be allowed. *Ask Chemicals*, 593 F. App'x at 510. The Court should therefore exclude Dr. Kulldorff's testimony about Dr. Tomljenovic's analysis in its entirety.

But even if the Court allows Dr. Kulldorff to confirm that Dr. Tomljenovic's math was correct, it should not allow Dr. Kulldorff to opine that her disproportionality analysis is anything more than it is—a tool for identifying safety signals. Analyses of adverse event reports can sometimes generate a "safety signal," which is a sign that an adverse event that "warrants further investigation."[4] But as the FDA notes, a safety signal raises only "a potential safety issue" and does not mean that "a causal relationship between the drug and the [] risk" exists.[5] Dr. Tomljenovic agrees and testified that her disproportionality analysis "should ***only*** be used for signal detection," not for calculating "a risk of adverse event in a general population." Ex. 9, Tomljenovic Dep. Tr. at 218:6–219:2 (emphasis added). Since Dr. Tomljenovic herself concedes this limitation of her analysis, Dr. Kulldorff should not be allowed to suggest that Dr. Tomljenovic's analysis can support any conclusions beyond safety signal detection. *See E.E.O.C. v. Freeman*, 778 F.3d 463, 472 (4th Cir. 2015) (noting that "trial judges may evaluate the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support" for the opinions).

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[4] Ex. 7, EMA, Glossary of Regulatory Terms – Safety Signal, available at https://www.ema.europa.eu/en/glossary-terms/safety-signal.

[5] Ex. 8 FDA, Potential Signals of Serious Risks, available at https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system

In sum, the Court should not allow Dr. Kulldorff to testify about Dr. Tomljenovic's disproportionality analysis because his opinions are improper parroting. But if the Court disagrees, it should not allow Dr. Kulldorff to testify that Dr. Tomljenovic's analysis is anything beyond a signal-generating analysis.

CONCLUSION

For these reasons, the Court should exclude Dr. Kulldorff's opinions about Merck's response to the EMA's Article 20 procedure and about Dr. Lucija Tomljenovic's disproportionality analysis.

DATED: January 6, 2025

Respectfully submitted,

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ARTIFICIAL INTELLIGENCE CERTIFICATION

I, Allyson M. Julien, certify the following with respect to Defendants' Memorandum in Support of Motion to Exclude the Expert Testimony of Dr. Martin Kulldorff Pursuant to Federal Rule of Evidence 702, in compliance with this Court's Standing Order, In Re: Use of Artificial Intelligence, dated June 18, 2024:

1. No artificial intelligence was employed in doing the research for the preparation of this document, with the exception of such artificial intelligence embedded in the standard on-line legal research sources Westlaw, Lexis, FastCase, and Bloomberg;
2. Every statement and every citation to an authority contained in this document has been checked by an attorney in this case and/or a paralegal working at his/her direction as to the accuracy of the proposition for which it is offered, and the citation to authority provided.

Dated: January 6, 2025

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